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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/680,284	10/06/2000	Sigrid Lise Fossheim	REF/FOSSHEIM/100	8494

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EXAMINER	
WELLS, LAUREN Q	
ART UNIT	PAPER NUMBER
1617	16

DATE MAILED: 05/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/680,284	Applicant(s) FOSSHEIM ET AL.	
	Examiner Lauren Q Wells	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6,9-11,24-26,31-37 and 39-68* is/are pending in the application.

4a) Of the above claim(s) *1-3,6,9-11,24-26,31-36,39-49,56-60,65 and 68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,50-55,61-64,66 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-3, 6, 9-11, 24-26, 31-37, and 39-68 are pending. Claims 1-3, 6, 9-11, 24-26, 31-36, 39-49, 56-60, 65, and 68 are withdrawn from consideration, as they are directed to non-elected subject matter. The Amendment filed 3/5/03, Paper No. 15, cancelled claims 4-5, 12-13, 23, 27-30, and 38, amended claims 1, 2, 6, 10, 11, 24, 26, 31, 32, 37 and added claims 39-68.

Applicant's arguments with respect to claims 37, 50-55, 61-64, 66-67 have been considered but are moot in view of the new ground(s) of rejection.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/5/03 has been entered.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-3, 6, 9-11, 24-2t, 31-36, 39-49, drawn to a method of imaging, classified in class 424, subclass 9.1.

II. Claims 37, 50-68, drawn to a contrast medium, classified in class 424, subclass 450.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the

product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product can be used as an imaging agent with a targeting compound that does not respond to a pre-selected physiological parameter.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Robert Chisholm on 3/31/03 a provisional election was made with traverse to prosecute the invention of Group II, claims 37, 50-68. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-3, 6, 9-11, 24-26, 31-36, 39-49 withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

The paper filed 1/14/02, Paper No. 7, elected phospholipids as the matrix/membrane material, paramagnetic compounds as the contrast generating species, MRI as the imaging technique, temperature as the physiological parameter, and cell adhesion molecules as the targeting ligand.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37, 50-55, 61-64, 66-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(i) The term "whereof" in claim 37 (line 2) is vague and indefinite, as it is confusing. Whereof what? Does Applicant mean thereof?

(i) The phrase "tissue electrical activity" in claim 50 (line 3) is vague and indefinite, as it is confusing. What is tissue electrical activity? Is it not ion concentration? Is Applicant claiming a range within a range? The specification does not define this phrase and one of ordinary skill in the art would not be apprised of its meaning.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 37, 50-55, 61-64, 66-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gamble et al. (4,728,575) in view of Ozer et al. (Eur. J. Pharm. Biopharm).

The instant invention is directed toward a contrast medium comprising a particulate material there particles comprising a matrix or membrane material and at least one magnetic resonance contrast generating species with the proviso that the magnetic resonance contrast

generating species is not a gas or gaseous precursor, and said matrix or membrane material being responsive to a pre-selected physiological parameter.

Gamble et al. teach contrast agents. Taught are micellular particles such as phospholipid vesicles which enclose a paramagnetic material. The vesicles may or may not have antibodies or other cell recognition targeting agents attached to the surface to provide specific targeting. Distearoylphosphatidycholine (DSPC), dipalmitoylphosphatidycholine (DPPC), and dimyritoylphophatidy choline (DMPC) are taught as vessel constituents. Gd and DTPA are taught as examples of paramagnetic materials. Specifically taught are DSPC/cholesterol vesicles comprising Gd-DTPA. The reference does not teach the liposomes as being sensitive to a pre-selected parameter. See abstract; Col. 2, line 59-Col. 3, line 22; Col. 5, line 15-Col. 6, line 44.

Ozer et al. teach temperature and pH-sensitive liposomes. The temperature-sensitive liposomes leak much more readily at the phase transition temperature of their membrane lipids. In vivo, such liposomes preferentially release encapsulated drug in a locally heated target area. Lipids are selected so as to make liposomes with liquid-crystalline phase transition temperatures a few degrees above physiological, near the range obtainable by local hyperthermia. The repeated passage of liposomes through the heated region and drug concentration causes the continuous release of drug content. The selection of temperature-sensitive liposomes is based on Tc. When a lipid bilayer is formed, the temperature at which release of encapsulated product occurs is always a few degrees lower than the bulk phase-transition temperature. The combination of temperature-sensitive liposomes with local hyperthermia seems a promising approach to achieve the targeting of drugs site-specifically. Optimization of the liposome preparation with respect to size, composition, and charge, and optimization of the temperature of

heating and by combining local hyperthermia with generalized hyperthermia to increase the available temperature range are necessary parameters. Table 1 provides examples of lipids that are typically used in such formulations and that have Tc values between 35 C and 80 C. See pages 97-100.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the teachings of Ozer et al. into the invention of Gamble et al. and obtain temperature sensitive liposomes because of the expectation of achieving a liposome product that exhibits controlled release in a site-specific manner.

Further, it is respectfully pointed out that lipids are known in the art to change conformation based on temperature. It is known that increasing the temperature increases the fluidity of lipids and hence, their leakage potential. Thus, one of skill in the art, without the teachings of Ozer et al., would be motivated to produce a liposome that is temperature sensitive because of the expectation of achieving a product that releases its contents in specific temperature ranges, i.e. in reaction to external heat or internal heat.

The Examiner respectfully points out that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). In the instant case, the phrase "for imaging of a physiological parameter" in claim 37 is not given patentable weight.

Notes

The term "dipalmitoylphosphatidyl-choline" in claim 68, line 4 is misspelled.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lauren Q Wells whose telephone number is (703) 305-1878. The examiner can normally be reached on M-F (7-5:30), with alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (703)305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

lqw
April 2, 2003

SREENI PADMANABHAN
PRIMARY EXAMINER 4/4/03